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Treatment of pernicious anemia

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Introduction

Any disease which receives the title of Pernicious deserves all of the time and intelligent and thorough investigation which is available to the medical profession. Such attention has that disease Pernicious Anemia received, at least during the past thirty years. The efforts of this exhausting study have born fruit, until at the present time the term pernicious, which is defined as "tending toward a fatal termination", is no longer applicable to this disease first described by Addison in 1849. Any paper dealing with the treatment of this disease must necessarily be a survey of the methods used since the first description of the disease in order to build up a logical and comprehensible basis for present day trends. Although current methods of therapy are a radical departure from those in years past, they still bear a hidden relationship and are based indirectly upon the previous work done.

The scope of this paper is quite limited, but in order to formulate some basis for treatment it is essential to give a brief outline of the general evolution from 1855 to the present time.

History

The disease entity now known as Pernicious Anemia was first described by Dr. Thomas Addison of Guy's Hospital. His first description was published in 1849 and six years later he published a detailed description of the disease as a preface to his work, On the Constitutional and Local Effects of Disease of the Suprarenal Capsule.[1] As a result of his work this type of anemia was most universally known as Addison's Anemia, which in the light of present day knowledge, even though not a descriptive title, is more appropriate than the term Pernicious.

Addison in reporting this disease has used the following descriptive terms: "Its approach is slow and insidious. The patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme. . . The countenance gets pale. The whites of the eyes become pearly, the general frame flabby rather than wasted. There is increasing indisposition to exertion with an uncomfortable feeling of faintness and breathlessness on attempting

it. . . The whole surface of the body presents a blanched, smooth, and waxy appearance; the lips, gums, and tongue seem bloodless. . . Appetite fails. . . Extreme languor and faintness supervene, breathlessness being produced by the most trifling exertion or emotion. . . The patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and a half torpid state, and at last expires." From this description is clearly seen the hopeless outlook which existed for Pernicious Anemia patients, and it is certainly not difficult to understand why such a disease should be termed pernicious.[2]

Granting the honor of priority, as far as adequate and primary description of the disease is concerned, to Dr. Thomas Addison, it still remains that many cases had been described previous to Addison's publications which undoubtedly fell clearly into the limitations of this disease. The most prominent case was reported in 1822 by a Scottish physician, Dr. J. S. Combe, and was given in such detail that there can be no doubt that it was an anemia of the pernicious type. This same case brought up the question in the mind of the author as to the possibility of special types of anemia. From the time when this case

was reported in 1822 until the second publication by Addison in 1855, many reports of cases, which in all likelihood fell into the category of Pernicious Anemia, appeared in the literature. Each case, although not definitely classified, did add something to the knowledge of the disease.[1]

Based upon the description given by Addison and others and because of the manifold group of findings elicited, a great many theories as to the primary site of affectation arose. As has always been the case (with occasional exceptions) in instances when the etiology of a disease is unknown there arises a multitude of theories as to the method of treatment. Each method being based upon the one finding or findings which to that particular investigator seems of primary consideration. And as is also the usual state when there are a great many therapeutic measures for a given disease, all are of doubtful value and none give absolute satisfaction.

This above generalization certainly applied to the therapeutic procedures in regard to Pernicious Anemia and continued to apply until 1926.

The general mode of treatment was fairly well stablized and has lasted, with certain modifications, up to the present time. Rest, the chief therapeutic measure which aids the

human body, was early recognized as of primary importance in Pernicious Anemia. Rest aids digestion, improves general oedema and tends to relieve severe mental strain.[3] Its chief purpose in Pernicious Anemia, however, lies in relieving cardiac stress. The heart in almost every case of Pernicious Anemia shows signs of strain, some fatty degeneration and some degree of dilitation.[1] All of these factors tend to decrease response to treatment. Any patient who is run down, has cardiac dilitation, poor digestive processes, and is in a state of mental unrest, is a very poor risk if these symptoms cannot be alleviated.

The value of fresh air and sunshine was well recognized and cold and dampness guarded against.[3] The ideas of the proper dietary control were far from uniform. Most men agreed upon a high caloric, nutritious diet, but specific types of food were not thought very important.[3] Pepper, in 1875, advised the use of food in its most easily assimilated forms, because of the degenerated state of the gastric mucosa which he found at post mortem. This same observation was made by Fenwick in 1877, and the subject of diet discussed as a very difficult one. Osler (1885) reported cases, "that appear to have got well with change of air and a better diet, after resisting all the ordinary measures."[1] By this it is

seen that diet was quite extensively considered by many men, but still its chief use at that time was that of generalized treatment.

Many drugs have been used in days past in a search for a specific but each seemed to fall short of the aim. Many of the drugs were scientifically used and were based upon sound physiology and pathology, and many are still used today as supportive measures. On the other hand the use of many of the drugs was founded upon false premises and was totally without any beneficial results.

Iron was one of the many drugs used. Its use depended upon its action on the formation of hemoglobin. We know that in Pernicious Anemia there is an abundance of Hemoglobin and iron stored in the body organs and its use therefore is unnecessary.[3]

There is one occasion, however, in the treatment of Pernicious Anemia in which iron is of value - this will be discussed later.

For the symptom or finding of Anacidity simple bitter tonics were given before meals and sometimes small doses of alkalies administered after meals.[2] Hydrochloric acid was given in fairly large doses during and following meals (4 c. c.) to make up for the lack of acidity.[1-3] Hydrochloric

acid was thought by many men to be a prophilactic measure against Pernicious Anemia since it had been shown that there was an absence of Hydrochloric Acid in cases of Pernicious Anemia and that individuals with no free Hydrochloric Acid were more prone to contract the disease. Dr. C. Beaumont Cornell as late as March 1929 reported a case in which the patient had been under strict Hydrochloric Acid prophilactic therapy and still developed Pernicious Anemia but promptly recovered under modern therapy.[4] Since this is only one case there can be no definite conclusion drawn.

Arsenic is another of the drugs which has been extensively used in Pernicious Anemia. For a long time its value was very highly regarded. Its value supposedly lay in its stimulating effect upon the hemopoetic system and its restraining action upon the destruction of blood. This action was questioned and no satisfactory confirmation has been given.[3] This drug was first employed in the treatment of Pernicious Anemia by Bramwell in 1877 and was the one therapeutic measure which was relied upon. The drug was administered as Fowlers solution, two to three drops, three times a day, and gradually increasing the dose until the symptoms of slight overdosage appeared. Then the

administration was stopped for from one to three days, then recommenced at two-thirds the maximum dose given, and this used as a maintenance dose. A fair percentage of cases seemed to respond to this form of treatment but eventually a relapse occurred. After each relapse the beneficial results obtained from this drug were considerably lessened.[1] In modern therapy arsenic has only a small place but is occasionally beneficial.

Much work has been done experimentally with vaccines and sera but these have offered nothing of value. Non-specific foreign protein injections have also failed to yield any beneficial results.[1]

Since in all cases of Pernicious Anemia there was found to be a disturbance of the bone marrow function the inclusion of this substance in the diet of Pernicious Anemia patients in a variety of forms has been tried.[3] Fresh red bone marrow was first used by Frazer in 1894. He reports using it in the treatment of one patient, giving doses of 100 grams each day over a long period of time. His results were quite favorable. Reports on the use of bone marrow are few and brief but all indicate beneficial response. The action of this substance is

very likely due to the same action as the present mode of therapy since the composition is so similar.[5]

Transfusion was the one procedure which was reputed of great value in Pernicious Anemia. It was known even at that time that a transfusion was not a cure for Pernicious Anemia but the results obtained more than justified its use. Its use greatly improves the general condition of the patient and retards the fatal issue which was inevitable until the radical changes which occurred after 1926. It was thought that transfusion increased the efficiency of the bone marrow, but later experience has shown that the bone marrow found in patients in which repeated transfusions had been used was more or less aplastic. It was not infrequently found that after several transfusions the hemolytic action in the patient's blood was so active that subsequent transfusion was of little and of only transient value. George R. Minot says, "In general, transfusion is the one therapeutic procedure from which definite benefit is to be expected in Pernicious Anemia."[3] Drs. Yates and Thalkimer, in the Journal of the American Medical Association December 25, 1926, reported a case of Pernicious Anemia which was treated by transfusion over a period of three years. This patient was able to

carry on a fairly normal existence but required one hundred-thirteen transfusions during that period. Each transfusion was between four and five hundred c. c. and averaged about one every two weeks.[6] Even today the use of transfusion has a definite place in the therapy of Pernicious Anemia although not in the same light as previously used. This will be discussed under the present day therapy.

Many surgical procedures have been tried including ileostomy, resection of the colon, and removal of the spleen. Splenectomy, however, was the chief surgical procedure which was used.[1] Splenectomy in Pernicious Anemia was based upon the assumption that the hemolytic cause of Pernicious Anemia resided in the spleen. Early in the history of Pernicious Anemia many favorable reports were made but Krumbharr's summary of results was particularly disappointing. The spleen is thought to have an inhibitory influence on bone marrow so that when splenectomy was done there was released the stored up products of the bone marrow. This fact, of course, leads to temporary beneficial results but it was found that Splenectomy by no means cured Pernicious Anemia, did not forstall a relapse or in any way alter the fatal cause of the disease. There were also many risks accompanying such a procedure. A patient with Pernicious

Anemia, a low blood count, and in very poor physical condition, is a poor surgical risk. Thrombosis following this procedure was common. In 70% of the cases reported by Minot in which splenectomy was done a definite temporary benefit was derived but at the decided risk of a definite mortality. He also made the observation that this procedure afforded more relief to the patients in which the spleen was exceptionally large.[3] Davidson and Gulland state that the only surgical procedures which have any place in the treatment of Pernicious Anemia are those performed for the eradication of septic foci. It has been found that Pernicious Anemia patients in which septic foci are present fail or respond much less to present day therapy.[1] This recommendation, therefore, is applicable to current therapeutic procedures.

The irradiation of the spleen was also experimented with, yielding somewhat similar results as splenectomy. F. Tomanec, in the British Journal of Radiology, August 1926, reported good results in twenty cases of Pernicious Anemia in which the spleen was irradiated with radium. He found that the time of remissions was considerably prolonged even in cases in which other methods of treatment had been ineffective. As a result of these reports he strongly

advised this procedure in preference to Splenectomy.[7]

After reviewing these methods of treatment in vogue previous to 1926 it is definitely clear that no specific therapeutic agent was known. Those which received the highest acclaim were at best only palliative and in no way served to alter the fatal course of the disease. Pernicious Anemia at that time was truly pernicious and the individual who was unfortunate enough to have developed this disease had far from a cheerful outlook for the future.

Work of Minot and Murphy

In 1926 one of the most radical changes in the field of medicine occurred in the method of treatment of Pernicious Anemia. This discovery is only rivaled by the isolation and adoption of insulin for the treatment of Diabetes Melitus. Although the change in the treatment took place almost overnight, the basis for the work dates back to the work of Whipple and Robscheit-Robbins.

In 1920 Whipple and Robscheit working on dogs to determine the available red cell pigment by observation of hemoglobin and blood volume made the following observations. On two successive days they removed one-fourth the blood volume, thus producing a uniform degree of anemia. These workers than observed the time interval necessary for the cell pigment to return to normal under varying dietetic conditions. Their results were as follows:

1. Four to seven weeks were required on ordinary table scraps.
2. Three to four weeks were necessary on liberal amount of meat and beef heart.
3. Two to four weeks were required to bring about marked response with cooked liver.

Jencks in 1922 making studies on blood regeneration found that regeneration was more rapid with protein than with either fat or carbohydrate when it was the sole source of food. They also found that vitamin rich diets were more favorable for rapid blood regeneration than any other diet containing only one food factor.[1]

Whipple and Robscheit-Robbins made further experiments in 1925. This time they produced a constant secondary anemia. The hemoglobin level was maintained at forty to fifty per cent by frequent bleedings. In these experiments, also with diet, the following results were obtained:

1. Beef liver gave maximal blood regeneration.
2. Beef heart less.
3. Beef muscle distinctly less.

Their conclusion: "Liver feeding in these severe anemias remains the potent factor for the sustained production of hemoglobin and red cells. This favorable and marked reaction is invariable in our dog experiments, no matter how long continued the anemia level, no matter how unfavorable the preceding diet periods may be, and regardless of the substances given with liver feeding."[1]

Also in 1925 Baker and Carrel by dietary experimentation found that lipoids had an inhibitory action on blood

regeneration. These men also, in 1926, suggested an important connection between blood regeneration and the inclusion in the diet of Vitamin A.[1]

It was upon the above foundation that the momental work of Minot and Murphy working in the Peter Bent Brigham Hospital on diet therapy in the treatment of Pernicious Anemia was based.

The report of their work appeared in the Journal of the American Medical Association, August 14, 1926. In beginning their paper, which is a review of forty-five cases on special dietary therapy in the Peter Bent Brigham Hospital of Boston, they acknowledge that their work is not new. However, the application of what had already been learned as to dietary effect on blood regeneration to humans is entirely the work of these two men.

They refer in their article to Habersham who in 1863, seven years following the second publication by Addison, found "Many patients at an early stage completely recover under the influence of bracing air and a stimulating diet." Later they refer to Burmer (1872) and Pepper (1875) who prescribed easily digested food because of the atrophic condition of the stomach nucosa in Pernicious Anemia. However, these two men placed no other emphasis on diet

other than general treatment. Osler in 1885 also observed "cases (of Pernicious Anemia) appear to have got well with change of air and a better diet after resisting ordinary means." Fenwick and Naegeli (1880) suggested diets sparing in farinacious food, but rich in protein. Hunter, ten years later, advised the opposite diet. Meat and green vegetables had long been used in treatment of Pernicious Anemia, but chiefly because they both contained iron and because meat contained blood. Until the time of this work the diets for Pernicious Anemia, had been those of a high caloric value and of a high nitrogen content. But despite all of the attention to diet little attention was paid to its influence on blood formation and destruction. All diets were of a general nature and specific foods had received no attention.

On the basis of the preceding findings Minot and Murphy placed their forty-five patients on what was known as the Murphy-Minot diet for Pernicious Anemia, which is as follows:

1. 120 to 240 grams or more of cooked calf or beef liver. Lambs kidney occasionally substituted.
2. 120 grams of mutton or beef muscle meat.
3. Not less than 300 grams of vegetables, especially

including lettuce and spinach - containing one to ten per cent carbohydrate.

4. 250 to 500 grams fruit.
5. 40 grams fat from butter or cream. Animal fats and oils were excluded.
6. If desired, an egg and 240 grams milk.
7. Dry and crusty bread, potatoes and cereals in order to allow a total intake of 2,000 to 3,000 calories, usually composed of 340 grams fat. Grossly sweet foods not allowed. Sugar permitted sparingly.

On this diet there was marked clinical improvement during the first two weeks. Not only was the reaction a clinical recovery but proven by the laboratory there was an actual physiological improvement.

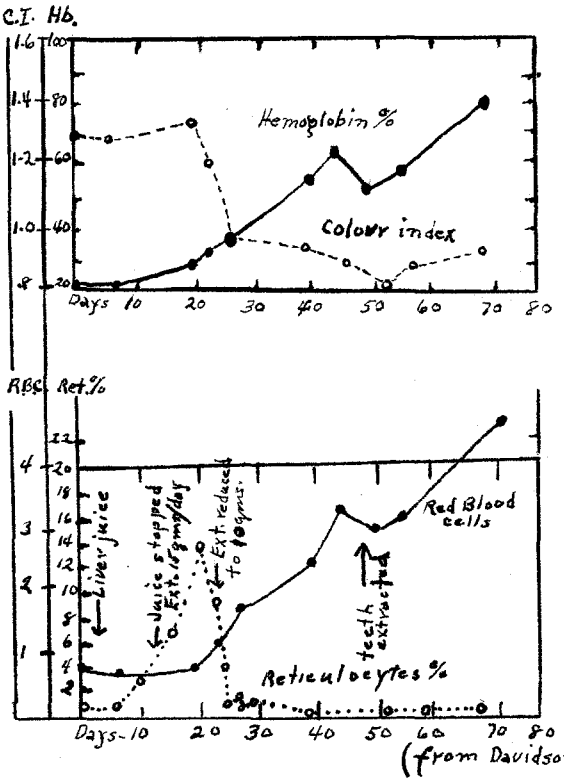
1. Rise of from one per cent to fifteen per cent (forty-five cases) in the reticulocytes count found in the peripheril blood stream. This was apparent by the end of the first week.
2. Even before the increase in reticulocytes there was a fall in the icterus index, indicating a lessening of blood destruction. This index had returned to normal within two to four weeks.

Average Red Blood Cell Count

Before Diet Started		1 month		2 months		3 months	
No. Cases	Average R.B.C. Count in Millions						
19	0.90	19	3.28	15	4.08	12	4.50
15	1.60	15	3.25	13	4.09	10	4.54
11	2.30	11	3.83	9	4.41	5	4.47
45	1.47	45	3.40	37	4.16	27	4.50

The above chart demonstrates the marked response to liver therapy as told by the red cell count. Additional data gathered by these investigators is as follows:

1. Improvement greatest in those cases in which there was the lowest initial counts.
2. That liver induced remissions reach a much higher peak than natural remissions.
3. That patients who had had several previous relapses did not respond to the diet as well as did the others.
4. Some patients who at first were unable to take liver well finally developed "ravenous appetities."
5. Bowel activity of all patients became more regular.
6. Nervous phenomena and the lack of Hydrochloric Acid were the only symptoms which failed to respond to liver therapy.
7. Information gathered suggested that patients who had had many transfusions may respond but slightly to the prescribed diet.[5]



(from Davidson & Gulland)

Graph illustrating effect of liver therapy in a case of Pernicious Anemia.

Note increase rate of blood formation following extraction of septic teeth.

As a result of this publication and due to the success which attended its use, Cecil says, "The dramatic success of liver diet in Pernicious Anemia has changed the entire outlook of this disease. Minot and Murphy, and since them many other investigators throughout the world, have reported brilliant results in applying to Pernicious Anemia Whipple's and Robscheit-Robbins' demonstrations that certain foods, especially liver, will induce rapid blood regeneration in dogs rendered anemic by bleeding.[8]

In April of 1927 another article by Murphy, Monroe and Fitz appeared in the Journal of the American Medical Association. This report was on cases in the Peter Bent Brigham Hospital from November 1925 to March 1926. These cases were chosen because of the marked degree of anemia which was present. Each patient was first confined to bed and the Murphy-Minot diet regime as previously outlined was prescribed. This diet was continued for the entire period of observation lasting several months. In addition to the diet regime each patient received from four to eight c. c. of dilute Hydrochloric Acid, three times a day. One patient was excepted to the latter medication. As far as possible all studies were made by one person at the same

time each day. These studies consisted of complete blood studies before and during treatment, hemoglobin determinations by Sahli method (15.6 grams for each 100 c. c. of blood considered normal), red and white cell and platelet counts. The histology of the cells was also studied.

The summary of this work: The results corroborated Minot and Murphy's observations that under proper dietetic care, a prompt, rapid and distinct remission of the anemia is produced in each instance. The diet appeared to cause delivery of new, young, red blood cells from the bone marrow into the general circulation, as evidenced first, by a prompt increase of reticulocytes in the circulating blood. At about the time that there was evidence of a marked reaction in the bone marrow there was a decrease of bile pigment concentration in the serum, as manifested by a fall in the icterus index. Coincidently there was an increasing red blood cell count and hemoglobin concentration, accompanied by a progressive growth in the blood tissue as a whole, as estimated by blood volume determinations.

The morphological appearance of the red cells under treatment became normal or essentially so; the color index became one or less than one; the average cell volume diminished and approached normal; the volume index and stroma index became normal.

The diet did not produce changes in non-protein-nitrogen of the plasma or in plasma protein. The protein of the corpuscles, however, increased notably and in almost direct proportion to the increasing hemoglobin concentration.[9]

In March 1929 a German by the name of Varga reported eight cases under treatment for Pernicious Anemia in which he made use of insulin in addition to the liver therapy. He used doses of from thirty to forty units of insulin, two times a day, stating that larger doses were unfavorable. His daily dosage of fresh liver or its equivalent was from 250 to 300 grams. He reports that all eight patients were in prostration and suffered from complete anorexia but the appetite returned immediately after use of insulin. The erythrocyte count increased from thirty to forty thousand each day, while the hemoglobin increased correspondingly, 0.5 per cent to one per cent each day. The only finding of Pernicious Anemia reported which did not respond to this type of therapy was the absence of free Hydrocloric Acid in the stomach.[10] Varga's basis for the use of insulin rests upon the assumption that Pernicious Anemia is the result of an acidotic condition in the body which facilitates hemolysis. If this assumption were correct insulin should be of benefit because of its action in increasing the alkalinity of the body fluids. Von Varga states that "insulin is an indispensible remedy

or adjudant to the standard liver therapy" in cases of Pernicious Anemia.[11]

This phenomenal response to liver treatment very naturally was the instigation for much investigation as to the active principal found in that substance. George Minot, in May 1929, gives the general conception of the active principle in liver. He says that it is a small nitrogenous base which acts to promote the growth of primitive red cells which crowd the bone marow in cases of Pernicious Anemia which are in relapse. He states that it is a water-soluble substance which is insoluble in ether and is precipitated by alcohol. He goes further in stating that it is very similar to Vitamin B, but is not one of the known vitamines.[12]

In 1932 Fontes and Thivolli give their views as to the action of liver. They show, to their satisfaction, that the anemia (working with animals) is due to a deficiency of histodine and tryptophane. They assume that since liver contains these two substances it is the addition of these which is of benefit in Pernicious Anemia. They treated patients with daily injection subcutaneously of histodine and tryptophane. In one of their cases the red blood cell count mounted to over five million within thirty

days. The other cases showed less rapid and less marked response to this treatment.[13]

Due to the marked distaste which some patients with Pernicious Anemia possess for liver the product of Cohn which is a liver extract containing the active principle of liver was a great boone for Pernicious Anemia treatment. This extract known as Liver Extract, Lilly 343, and recognized as a valuable product by the American Medical Association and the Council on Pharmacology and Chemistry is non-protein in nature; is free from carbohydrate, lipoids and iron. The effective substance is thought to be a polypeptid or a nitrogenous base. Dakin, West, and Howe are of the opinion that the active principle is a compound of Beta-hydroxy-glutamic acid and hydroxy-proline. Whatever the active principle might be, the use of Cohn's extract was accompanied by as remarkable results as was the use of whole liver. According to Sturgis and Riddle the use of large doses of the extract (20 vials) produces a marked reticulocyte count within forty-eight hours. Pulfer and Reznickoff reported good response from rectal administration, thus giving another advantage over whole liver.[14]

Following upon the discovery of the advantage of liver many investigators began to experiment with other glandular

substances which closely resembled liver. Ungley reports four such cases in which brain substance either fresh or desiccated was used in place of the liver. His results were as follows:

1. Response obtained in all four patients.
2. Potency about one-third that of liver.
3. Was as effective or more so than liver if combined degeneration of the cord was present.[13]

Because of the fact that fetal hemoglobin production is in the placenta this substance was tried and Mach reports good response in two patients although not as marked as under liver therapy.[13]

As has already been mentioned the active principle of liver closely resembles Vitamin B in composition. Working upon this fact Davidson treated four cases of Pernicious Anemia with a substance called Marmite, which contains Vitamin B. These efforts were unsatisfactory, however, since no response was obtained in three of the four and the exception was already passing into a natural remission.[13]

Since the work of Minot and Murphy it has been proven many hundreds of times that liver therapy in Pernicious Anemia is a specific for that disease. This success has led to the following statement by George Minot, "the successful treatment of Pernicious Anemia rests on the daily

ingestion throughout life of a potent material contained in mammalian liver and certain other foods (kidney)[8]". An aphorism has arisen which is agreed upon by most clinicians throughout the world in regard to liver therapy. "An anemia which will not respond to liver is not Pernicious Anemia." This statement has few exceptions. But, as has been pointed out previously, in patients in which Pernicious Anemia is of long standing and in which repeated blood transfusionshave been given the bone marrow becomes aplastic and the subsequent use of liver awakes little or no response in the bone marrow. It is in such cases that blood transfusions are still the sole means of treatment.

It might be well here to outline the present day method of liver therapy as given by Osler.[15] Several changes have taken place since the original work of Minot and Murphy. Such an elaborate diet has been found unnecessary. For example, the high protein diet and fat free diet are no longer considered essential since it has been shown that patients will show marked response on liver alone with a normal diet which supplies only the essential coloric value.

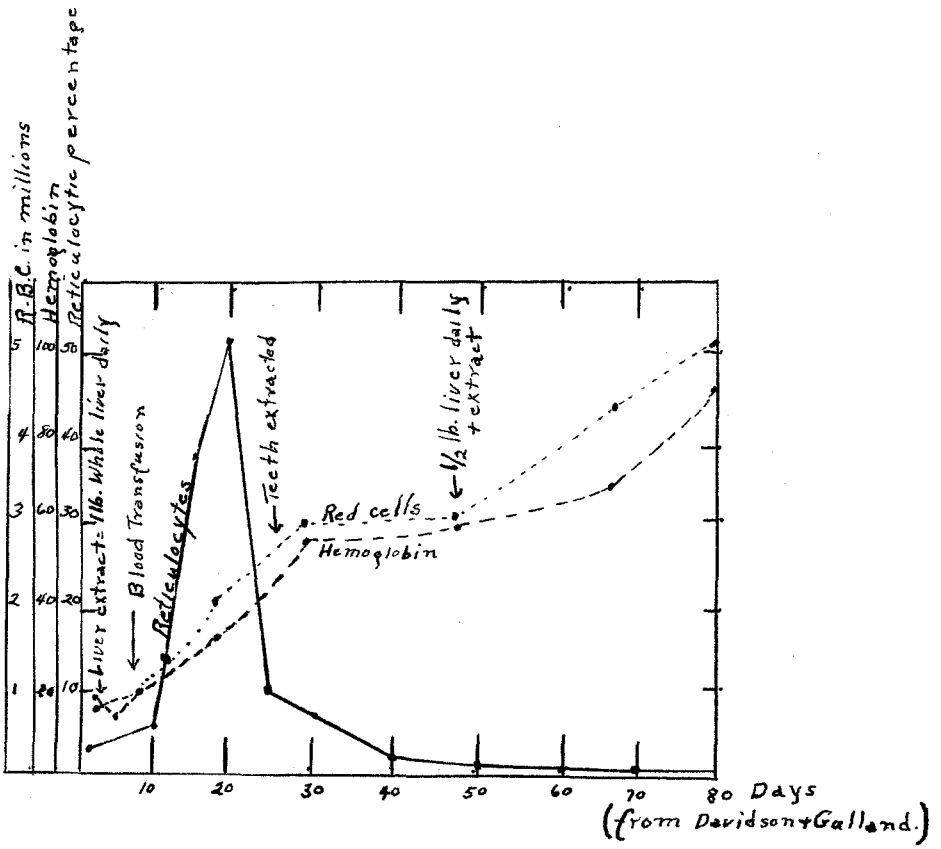
Osler's method of treatment in outline:

1. Patient kept in bed until marked improvement.
2. Plenty of fresh air and sunshine.

3. Liver and kidney of specific value.
4. Liver one-half pound each day, or liver extract of proven potency (equivalent of one-half pound of fresh liver each day in three doses.)
5. Watch for digestive disturbances such as diarrhea and constipation.
   a. Reduce diet in diarrhea.
   b. Enema in cases of constipation.
6. Fowler's solution, three c. c., three times a day, is the drug of greatest value.
7. Dilute Hydrochloric Acid in full doses drams one (four c. c.) during and after meals.
8. Care of focal infections (mouth and teeth). It has been found that the presence of focal infection greatly retards the response to liver therapy.
9. Ultra-violet and insulin advocated in small doses - five to ten units, twice a day.
10. After improvement, monthly check-up on blood.
11. Transfusion is now required only in very grave conditions when patient is first seen, in order to tide over until liver therapy can bring results, or in cases of aplastic bone marrow.

Cecil adds the following measures:

1. Sedatives when indicated.
2. Potassium Chlorate mouth wash to relieve the glossitis.[8]



(from Davidson + Galland.)

Graph showing the effect of a combination of liver extract therapy and blood transfusion.

It has been found that liver and liver extract whether given orally, subcutaneously, intravenously or rectally produce the following results:

1. Gastro intestinal tract.
    a. A relief and disappearance of the glossitis.
    b. No effect on the Hydrochloric Acid content of the stomach.
    c. Relief of disorders such as constipation and diarrhea.
    d. Increase in appetite.
2. Circulatory system
    a. At first an increase in reticulocyte count.
    b. Later increase in normal erythrocytes and the disappearance of the abnormal forms and an increase in blood platlet count.
    c. A marked decrease in the icterus index.
    d. Recovery of hear depends upon degree of fatty degeneration which has resulted from the anemia.
    e. Oedema quickly relieved.
3. Muscular system.
    a. Tone of muscles increases.
    b. General weakness disappears.

4. Nervous system.
    a. Liver prevents progress of nervous changes.
    b. Smithburn and Zerfas in reporting one hundred fifteen cases with nervous involement show
        (1) Numbness and tingling easily improves.
        (2) Ataxia definitely improved.
        (3) Psychosis not definitely affected.[13]

In addition to the active treatment of Pernicious Anemia with liver, it is essential to determine a maintenance dosage, for Pernicious Anemia like diabetes, is not cured but is held in check by the treatment which must be continued throughout life. The dosage is reduced when the blood picture returns to normal. This amount is determined by trial based upon blood analysis. It has been found that the average weekly maintenance dose is about 300 grams of liver or its equivalent.[14]

In cases in which there is a failure of response to liver therapy, several factors may be responsible:

1. Wrong diagnosis.
2. Infections or complicating disease (arteriosclerosis)
3. Inactive substance or inadequate doses.
4. "Absortive relapses" symptoms appear even with a normal blood picture.

5. Aplastic bone marrow resulting from

a. Too many transfusions.

b. Bone marrow exhaustion.[14]

A few cases have been reported in the literature of ill effects produced by a high liver diet. "Minot and Murphy, and also Spence, in 1927, reported the occurrence of arthritic symptoms and attacks of 'gout' in two or three cases." . . "Purines undoubtedly are dangerous substances when eaten excessively by persons with raised blood pressure, but fortunately the great majority of Pernicious Anemia cases have a very low blood pressure, and this treatment is of value in bringing the level up to normal. Neither Minot nor ourselves (Davidson and Gulland) have found any ill effects on blood pressure produced by liver feeding. In the only three cases of Pernicious Anemia which we have seen with a high blood pressure, we took the precaution of treating them with liver extracts, since these substances are practically non-nitrogenous. No ill effects were produced on the renal system in any case in which no abnormality existed previous to treatment. One case with chronic interstitial nephritis died of uraemia, and in another case of severe hemolytic anemia of pregnancy an acute nephritis was started by liver treatment. This patient had had eclamptic symptoms, and showed evidence of renal damage previous to parturition. Liver treatment was

stopped for a few days, and extract substituted with excellent results. Where any suspicion of renal inefficiency exists, extracts should be used in preference to whole liver."[1]

"The dietetic treatment of Pernicious Anemia has won a remarkable therapeutic victory for the science of medicine in its battle against disease. One again the cooperation of experimental and clinical research has achieved an effect which would have been impossible by individual effort."[1]

Other Therapeutic Measures

The high cost of liver extracts led to the experimentation, instigated by Minot, by Bowie and Castle. Castle was associated with Minot at the Thorndike Memorial Laboratory and for that reason could not help but be deeply interested in this new work on the treatment of Pernicious Anemia. Basing their work upon that done by Cohn in preparing his liver extract, Castle and Bowie began making liver stews and brews, thus bringing this life-saving measure to the humblest sufferers as well as those in better financial circumstances.[14]

Once interested in this great experiment Castle did not stop, but using himself as a laboratory animal, he was able to procure this miraculous life-saving agent from still another source than from liver. He based his experiment upon the supposition that the etiological factor in Pernicious Anemia lay in a deficiency in the stomach composition of those people who had the disease. From this he reasoned that this unknown substance which was therapeutic for Pernicious Anemia must be present in the stomach of normal individuals; or that the stomach of normal individuals did something to food which the abnormal stomach in Pernicious Anemia was unable to do.[2.]

With these thoughts in mind Castle daily, on an empty stomach, ate rare hamburger steak, and by emptying

the stomach found that this unknown therapeutic agent was present. He found that the reaction in Pernicious Anemia patients to this substance was just as remarkable as their response to liver diets.[2]

Again basing their work upon this finding made by Castle, Dr. Sturgis and Isaacs working at the University of Michigan went a step further and produced what is now known as ventriculin, dried powdered pig stomach.[2]

Soon after the introduction of Ventriculin many men reported favorable results with its use. It brought about a response in the hemopoietic system similar to that produced by liver and had the advantage of having very little taste. It was found that a dosage of from 15 to 30 grams each day was sufficient to bring about a reticulocyte response.[14]

Sturgis and Isaacs tested their product by using it in a series of 50 patients using 50 more patients on liver diet as controls. Their results showed the action of the two to be approximately the same. One of their cases, however, which did not respond to liver therapy gave a very marked reaction to Ventriculin.[13]

Wilkinson reports 108 cases of Pernicious Anemia in which the therapeutic agent used was dessicated hog stomach. They found that all patients responded favorably and that seven of the 108 patients produced over six million red blood cells for each cubic milimeter of

blood. Other findings follow:

(1) Fifty percent complained of some parasthesia of hands and feet. These were entirely relieved in a majority of the cases.

(2) Eight of the patients with definite Posteric-lateral column involvement and altered reflexes-three improved and returned to heavy work-four were much improved but not working, only one showed no change.

(3) Forty-seven cases in which liver was compared with hog stomach.

(a) Hemoglobin increased 1.4 times more rapidly with hog stomach than with liver.

(b) Red blood cell count increased 1.7 times more rapidly with hog stomach than with liver. (The fallacy lies in inadequate liver dosage.)[13]

Isaacs and Sturgis in a later report (Journal of the American Medical Association, August 23, 1930) cite 39 cases of Pernicious Anemia in which dried defatted hog stomach was used. They found that remissions could be produced by the use of 15 grams of the preparation (corresponding to 100 grams of fresh hog stomach). They also observed that the remission could be maintained by as little as seven grams of the material given daily. In working out a guide as to dosage they report:

(1) Safe clinical dosage is 10 grams for each million red blood cell deficit.

(2) Maintenance dose is 10 grams, five to seven times each week.

They also corrected their earlier statement as to the relative efficiency of hog stomach and liver, stating them to be of equal value.[16]

Further work was carried out by Conner and reported in the Journal of the American Medical Association February 14, 1931. In his work he treated 60 Pernicious Anemia patients with gastric tissue of swine or with tripe. Tipe was given to only two of these patients and unsatisfactory results were obtained. These two patients were later given the gastric juice of swine and responded well. Raw and dried hog stomach was used with equal results. They also fed whole gastric wall, mucosa, and the remainder after the mucosa was removed. All of these factions gave satisfactory results, proving that the muscle meat was not essential to produce a response.[17]

Castle later, working with the liver extract of Cohn, found that a certain faction (faction G) was suitable for intraveous injection. He found that a single injection of this faction (the amount obtained from 100 grams of liver) was sufficient to bring about a maximal reticulocyte response. He recommends this method of administration in very sick patients or in very resistant cases.[18]

Conclusion

From this very meager survey of the literature dealing with the treatment of Pernicious Anemia from Addison's time up to the present, the very remarkable and beneficial contribution made to medicine, and to those unfortunates who suffer from Pernicious Anemia, by Minot and Murphy in 1926 is self-evident. It has lifted Pernicious Anemia out of the class of which Osler says, "..... maladies, against which we have and can scarcely ever hope to have a curative measure. . . ." It was this work which made Pernicious Anemia no longer pernicious and gave back to many men and women the expectancy of a normal and productive existance. The work in this field is not finished but only begun; we have seen much advance since the advent of liver therapy, including extracts which can be given orally, intravenously, subcutaneously, or rectally, and more recently the addition of Ventriculin, and other similar products, which augment the use of liver. It is work and contributions such as this that justify the untiring effort and unfruitful toil of many of the struggling research men in the medical profession, and which serves to push medicine ahead, making it better able to care for the ills of mankind.

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